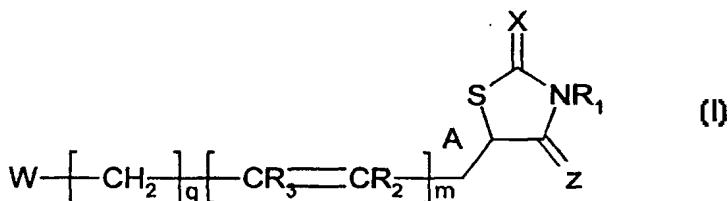




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(21) International Application Number: PCT/EP99/07252 (22) International Filing Date: 30 September 1999 (30.09.99) (30) Priority Data: 98118539.0 30 September 1998 (30.09.98) EP (71) Applicant (for all designated States except US): ROCHE DIAGNOSTICS GMBH [DE/DE]; D-68298 Mannheim (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): ESSWEIN, Angelika [DE/DE]; Birkenweg 4, D-64572 Büttelborn (DE). SCHAEFER, Wolfgang [DE/DE]; Tannhaeusering 190, D-68199 Mannheim (DE). TSAKLAKIDIS, Christos [GR/DE]; Huegelstrasse 1/1, D-69469 Weinheim (DE). HONOLD, Konrad [DE/DE]; Suedstrasse 24, D-82377 Penzberg (DE). KALUZA, Klaus [DE/DE]; Hochfeldanger 3, D-83670 Bad Heilbrunn (DE). (74) Common Representative: ROCHE DIAGNOSTICS GMBH; Patent Dept., D-68298 Mannheim (DE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: THIAZOLIDINE DERIVATIVES FOR THE TREATMENT AND PREVENTION OF METABOLIC BONE DISORDERS

**(57) Abstract**

The object of the present invention are compounds of general formula (I), in which: m signifies a number between 0-8; q signifies a number between 0-8; A signifies a single or double bond; R₁ signifies hydrogen or, when X and Z are oxygen, also -(CH₂)-COR₄ with a =0-6; R₂, R₃ signify hydrogen or lower alkyl, whereby R₂ and R₃ can be the same or different and, when m signifies 2-8, R₂ and R₃ in the group CR₂=CR₃ can have various significances within the following sequence; R₄ signifies hydroxyl, lower alkoxy or the NR₁R₂ residue, whereby R₁ and R₂ can be the same or different; X signifies oxygen or imino; Z signifies oxygen, sulfur or imino; W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments for the prophylaxis or therapy of metabolic bone disorders.

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Thiazolidine derivatives for the treatment and prevention of metabolic bone disorders

The present invention is concerned with thiazolidine derivatives for the treatment and prevention of metabolic bone disorders, a process for their manufacture as well as medicaments which contain these compounds.

In healthy persons the synthesis and degradation processes in bones is almost in equilibrium, i.e. the activity of the osteoblasts and osteoclasts is balanced. However, if this equilibrium is disturbed in favour of the osteoclasts and/or to the detriment of the osteoblasts, this leads to a reduction in the bone mass and to a negative change in the bone structure and function.

Hitherto, bone resorption inhibitors such as oestrogens, calcitonin and biphosphonates have primarily been used for the treatment of metabolic bone disorders. The use of these substances is, however, limited and also does not show the desired effect in all cases. Compounds which have a stimulating activity on bone synthesis and in addition contribute to an increase in an already reduced bone mass are accordingly of especial significance for the treatment of metabolic bone disorders.

Compounds having the thiazolidine structural element are known as antidiabetics, cytostatics inflammation inhibitors and for the treatment of cardiovascular illnesses and bacterial infections, with the treatment of osteoporosis in addition to an antidiabetic activity also being described in Applications EP 783888, EP 590793, EP 676398 and EP 708098.

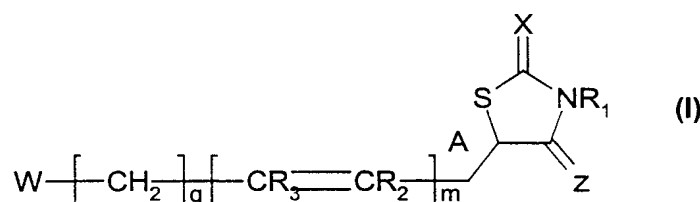
The parathyroid hormone (PTH), a hormone from the parathyroid gland, is the natural ligand of the receptor and an important regulator for the maintenance of the calcium level in the body. PTH can stimulate bone formation or bone resorption. In this, it acts as a regulatory hormone on a series of enzymes, inter alia, on adenylate cyclase (cAMP synthesis) and on ornithine decarboxylase. PTH mobilizes calcium from bones in the case of calcium deficiency, reduces calcium excretion from the kidneys and

simultaneously improves the resorption of calcium from the intestine by an increased synthesis of $1,25-(\text{OH})_2\text{D}_3$. A normalization of the calcium level is achieved by the action on these target organs. On the other hand, the incorporation of calcium in bones is stimulated in the case of an elevated calcium level. This osteoanabolic activity of PTH and its fragments has been attributed to the activation of adenylate cyclase and of cAMP-dependent protein kinases (Rixon, R. Whitfield, J. et al JMBR 2 (8) 1179-89 (1994)).

Surprisingly, it has now been found that thiazolidine of the present invention stimulate the PTH receptor-mediated cAMP formation. Compounds of the present invention are accordingly suitable for the broad treatment of metabolic bone disorders. They can be used primarily to good effect where the bone synthesis is disturbed, i.e. they are especially suitable for the treatment of osteopenic disorders of the skeletal system such as e.g. osteoporosis, inter alia, osteogenesis imperfecta as well as for the local assistance in bone regeneration and osteoinduction such as e.g. in orthopedic and maxillary medical indications, in fracture healing, osteosyntheses, pseudoarthroses and for the healing in of bone implants. However, having regard to these properties they also find use in the prophylaxis of osteoporosis.

By their influence on bone metabolism medicaments with the thiazolidine of the present invention as active substances furthermore form a basis for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis.

The object of the present invention are compounds of general formula (I),



in which

- 30 m signifies a number between 0-8,
 q signifies a number between 0-8

- A signifies a single or double bond
- R₁ signifies hydrogen or, when X and Z are oxygen, also -CH₂)-COR₄ with a = 0-6
- R₂, R₃ signify hydrogen or lower alkyl, whereby R₂ and R₃ can be the same or different and, when m signifies 2-8, R₂ and R₃ in the group CR₂=CR₃ can have various significances within the following sequence
- R₄ signifies hydroxy, lower alkoxy or the NR₁R₂ residue, whereby R₁ and R₂ can be the same or different
- X signifies oxygen or imino
- Z signifies oxygen, sulphur or imino
- W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

As a rule, lower alkyl signifies linear or branched alkyl residues with one to six carbon atoms, preferably methyl, ethyl, propyl, i-propyl, butyl, t-butyl, pentyl, hexyl, particularly methyl.

Alkoxy groups signify a combination of a C₁-C₁₀-alkyl group in accordance with the above definition with an oxygen atom, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentoxy groups.

Under monocycle there are to be understood optionally mono- or polysubstituted, saturated or unsaturated ring systems with 3-8, preferably 5-7 carbon atoms, which optionally can be interrupted by one or more hetero atoms, such as nitrogen, oxygen or sulphur, especially the phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, morpholinyl, thiamorpholinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, furyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl residue, as well as residues such as e.g. phenyl phenyl ether, diphenylmethane and biphenyl. As substituents there come into consideration primarily lower alkyl, alkylcarbonyl, alkoxy, alkoxy-carbonylalkoxy, amino, benzyl, benzyloxy, carboxyl, dialkylamino, dioxymethylene, diphenylamino, hydroxy, mercaptoalkyl, phenoxy, styryl and halogen.

In the case of the bicycle set forth under W, this is preferably a residue such as the naphthyl, tetrahydronaphthyl, decalinyl, quinolinyl, chromane, chromene, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, indazolyl,

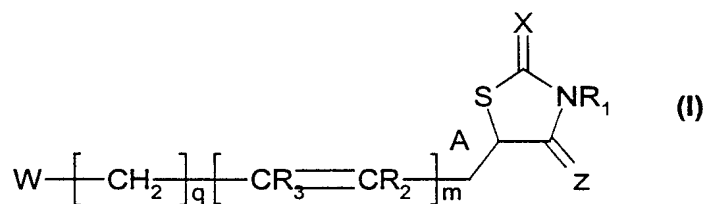
oxindolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl or purinyl residue, especially the indolyl, naphthyl, benzimidazolyl, quinolinyl, tetrahydroquinolinyl benzothiophenyl and benzofuranyl residue, which optionally can be mono- or polysubstituted. As substituents there come into consideration primarily
 5 lower alkyl, alkylcarbonyl, alkoxy, alkoxycarbonylalkoxy, amino, benzyl, benzyloxy, carboxyl, dialkylamino, dioxymethylene, diphenylamino, hydroxy, mercaptoalkyl, phenoxy, styryl and halogen.

In the case of the tricycle set forth under W, this is preferably a residue such as the
 10 anthracene, fluorene, dibenzofuran or carbazole residue.

Compounds of formula I wherein W is phenyl, naphthyl, indolyl, benzofuranyl or benzothiophenyl, X is oxygen, m and g are both 0 and R₁ is hydrogen are disclosed in EP-A-0434394 however for the treatment of inflammatory lowel diseases.

15 Compounds of formula I wherein W is an amino substituted phenyl or indolyl, X is imino, m and q both are 0 and R₁ is hydrogen are disclosed in USP 5.143.929, however for the treatment of inflammatory.

20 Therefore subject of the present invention are also new compounds of general formula I



in which

- 25 m signifies a number between 0-8,
 q signifies a number between 0-8
 A signifies a single or double bond
 R₁ signifies hydrogen or, when X and Z are oxygen, also -CH₂)-COR₄ with a = 0-6
 R₂, R₃ signify hydrogen or lower alkyl, whereby R₂ and R₃ can be the same or different
 30 and, when m signifies 2-8, R₂ and R₃ in the group CR₂=CR₃ can have various significances within the following sequence

- R₄ signifies hydroxy, lower alkoxy or the NR₁R₂ residue, whereby R₁ and R₂ can be the same or different
- X signifies oxygen or imino
- Z signifies oxygen, sulphur or imino
- 5 W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl, naphthyl, indolyl, benzofuranyl and benzothiophen-yl, if X signifies oxygen, m and q are both 0 and R₁ is hydrogen,

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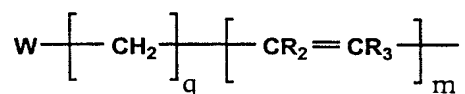
whereas W is not an aminosubstituted phenyl and indolyl, if X signifies imino, m and q both are 0 and R₁ is hydrogen,

- as well as their physiologically compatible salts, esters, optically active forms, racemates,
- 15 tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments.

- Preferred are compounds of general formula (I) in which m signifies a number between
- 20 0 and 4, q signifies the number 0 or 1, A signifies a double bond, R₁ signifies hydrogen or a group -(CH₂)_a-COR₄, a preferably signifies a number between 1 and 3, R₄ signifies hydroxyl, methoxy or ethoxy, R₂ and, respectively, R₃ signify hydrogen or methyl, X and Z signify oxygen and W signifies an optionally mono- or polysubstituted naphthalene, phenyl, thiophene, indole, furan, benzothiophene, cyclohexenyl or biphenyl residue.

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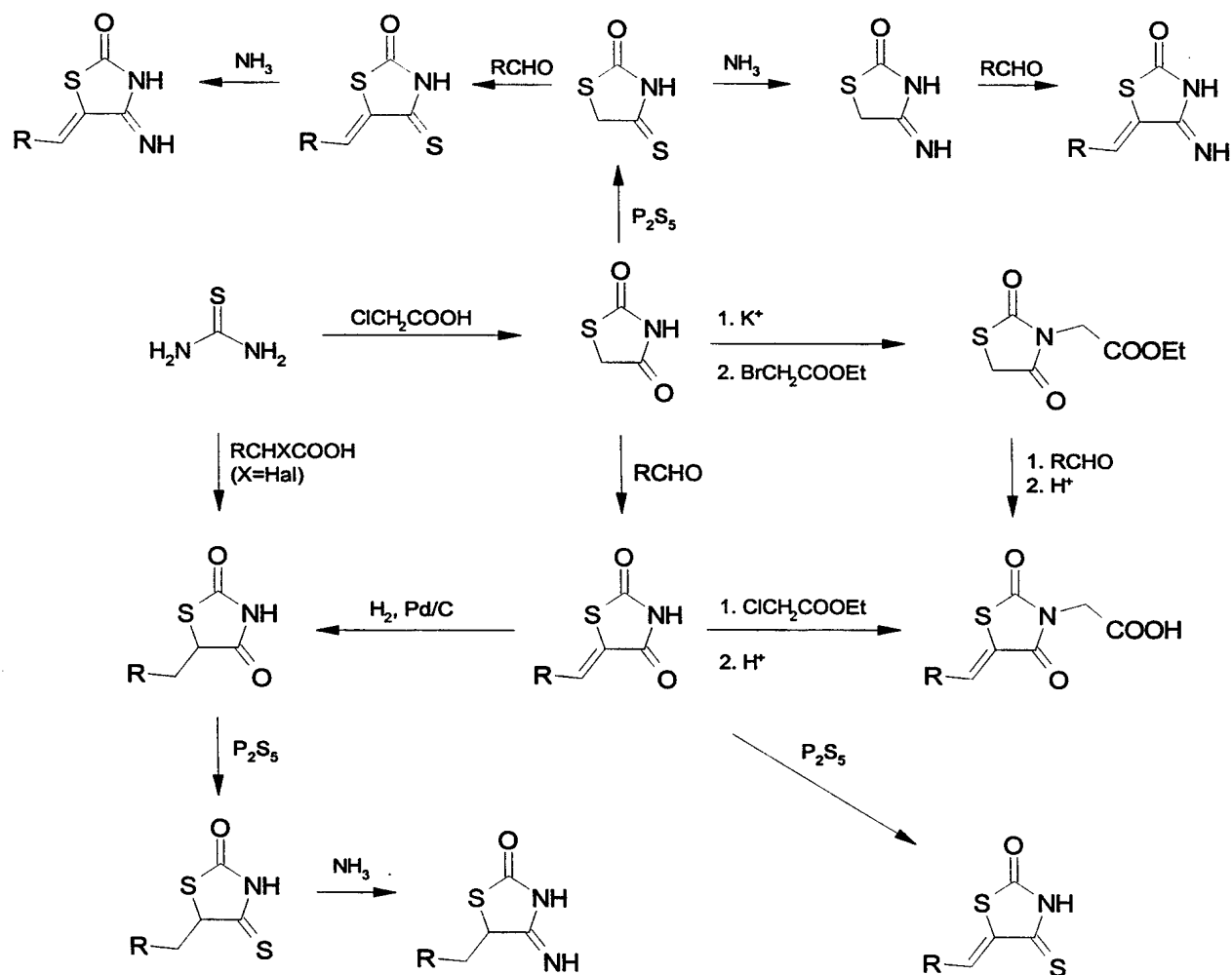
The manufacture of the compounds of general formula (I) is possible according to methods known per se. An overview of the methods of synthesis is set forth in Schemes 1 and 2; whereby R signifies the group:



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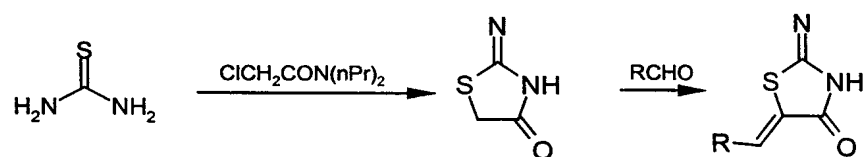
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Scheme 1



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Scheme 2



The α -halocarboxylic acids and aldehydes used as starting materials are either commercially available, known or can be prepared analogously to the generally known processes.

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Compounds of formula (I) can be administered (sic) in liquid, solid or aerosol form orally, enterally, parenterally, topically, nasally, pulmonary or rectally in all usual non-toxic pharmaceutically acceptable carrier materials, adjuvants and additives. The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The term parenteral embraces subcutaneous, intravenous and intramuscular delivery or infusions. Oral administration forms can be e.g. tablets, capsules, dragees, syrups, solutions, suspensions, emulsions, elixirs etc., which can contain one or more additives from the following groups, such as flavourings, sweeteners, colouring agents and preservatives. Oral administration forms contain the active ingredient together with non-toxic, pharmaceutically acceptable carrier materials which are suitable for the production of tablets, capsules, dragees etc., such as e.g. calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; starch, mannitol, methylcellulose, talc, highly dispersible silicic acids, high molecular fatty acids (such as stearic acid), groundnut oil, olive oil, paraffin, miglyol, gelatine, agar-agar, magnesium stearate, beeswax, cetyl alcohol, lecithin, glycerol, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycol). Tablets, capsules, dragees etc. can be provided with an appropriate coating, e.g. glyceryl monostearate or glyceryl distearate, in order to prevent undesired side effects in the gastrointestinal tract or to give a longer duration of action by the delayed absorption in the gastrointestinal tract. As the injection medium there are preferably used sterile injectable aqueous or oily solutions or suspensions which contain the usual additives such as stabilizers and solubilizers. Such additives can be e.g. water, isotonic saline, 1,3-butanediol, fatty acids (such as oleic acid), mono- and diglycerides or miglyol. For rectal use there can be used all suitable non-irritating additives which are solid at normal temperatures and liquid at rectal temperatures, such as e.g. cocoa butter and polyethylene glycol. Pharmaceutically usual carrier media are used for application as aerosols. Creams, tinctures, gels, solutions or suspensions etc. with the pharmaceutically usual additives are used for external application. The dosage can depend on a variety of factors such as mode of administration, species, age and/or individual condition. The doses to be administered daily or at intervals lie at 1-

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1000 mg/individual, preferably at 10-250 mg/individual, and can be taken at one time or divided over several times.

The compounds of formula (I) can also be applied locally to/in the bones (optionally
5 with surgical intervention). The application directly to/in the bones (optionally with surgical intervention) can be effected locally or carrier-bonded either in solution or suspension, conveniently by infusion or injection. Carrier-bonded compounds of formula (I) can be administered, for example, as gels, pastes, solids or as a coating on implants.

10 Biocompatible and preferably biodegradable materials are used as the carrier. Preferably, the materials themselves also induce wound healing or osteogenesis.

For local application it is preferred that the compounds of formula (I) are imbedded in
15 polymer gels or films in order to immobilize them and to apply these preparations directly on the site of the bone to be treated. Such polymer-based gels or films consist, for example, of glycerine, methylcellulose, hyaluronic acid, polyethylene oxides and/or poloxamers. Also suitable are collagen, gelatines and alginates and are described, for example, in WO 93/00050 and WO 93/20859. Further polymers are polylactic acid
20 (PLA) and copolymers of lactic acid and glycolic acid (PLPG) (Hollinger et al., J. Biomed. Mater. Res. 17 71-82 (1983)) as well as the bone derivative "Demineralized Bone Matrix" (DBM) (Guterman et al. Kollagen Rel. Res. 8 419-4319 (1988)). Also suitable are polymers as are used, for example, for the adsorption of TGF β and which are described in EP-A 0 616 814 and EP-A-0 567 391 and synthetic bone matrices in
25 accordance with WO 91/18558.

Likewise suitable as carriers for the compounds of formula (I) are materials which are usually used for the implantation of bone substitutes or otherwise of therapeutically active substances. Such carriers are based, for example, on calcium sulphate, tricalcium
30 phosphate, hydroxylapatite (sic) and its biodegradable derivatives and polyanhydrides. Apart from these biodegradable carriers there are also suitable carriers which are not biodegradable, but which are biocompatible. Such carriers are, for example, sintered hydroxylapatite, bioglass, aluminates or other ceramic materials (e.g. calcium aluminium phosphate). These materials are preferably used in combination with the
35 biodegradable materials, such as especially polylactic acid, hydroxylapatite, collagen or

tricalcium phosphate. Further non-degradable carriers are described, for example, in US Patent 4,164,560.

It is especially preferred to use a carrier which liberates the compounds of formula (I) continuously at the target site. Especially suitable for this are e.g. "slow release pellets" from Innovative Research of America, Toledo, Ohio, USA. Pellets which release the compounds of formula (I) over several days, preferably up to 100 days with a daily dosage of 1-10 mg/kg per day, are especially preferred.

Preferred in the scope of the present invention are, apart from the compounds named in the Examples and compounds derivable by a combination of all of the significances of the substituents set forth in the claims, the following derivatives as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments,

Preferred Compounds (PC):

1. 5-(9H-Fluoren-2-ylmethylene)-thiazolidin-2,4-dione
2. 5-Phenanthren-9-ylmethylene-4-thioxo-thiazolidin-2-one
3. 5-Anthracen-9-ylmethylene-4-imino-thiazolidin-2-one
4. 2-Imino-5-(10-methyl-anthracen-9-ylmethylene)-thiazolidin-4-one
5. [5-(3-Furan-2-yl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
6. 5-Benzyl-thiazolidin-2,4-dione
7. 5-[3-(2-Methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
8. 5-(2,3-Dimethoxy-benzylidene)-thiazolidine-2,4-dione
9. 4-Thioxo-5-(2,3,4-trimethoxy-benzylidene)-thiazolidin-2-one
10. 5-(2,4-Dimethoxy-benzylidene)-4-imino-thiazolidin-2-one
11. 2-Imino-5-(2,4,5-trimethoxy-benzylidene)-thiazolidin-4-one
12. [2,4-Dioxo-5-(2,4,6-trimethoxy-benzylidene)-thiazolidin-3-yl]-acetic acid
13. 5-(2,5-Dimethoxy-benzyl)-thiazolidine-2,4-dione
14. 5-[3-(2-Ethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
15. 5-(2-Hydroxy-benzylidene)-thiazolidine-2,4-dione
16. 5-(2-Hydroxy-3-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
17. 5-(3-Ethoxy-2-hydroxy-benzylidene)-4-imino-thiazolidin-2-one

18. 5-(2,3-Dihydroxy-benzylidene)-2-imino-thiazolidin-4-one
19. [2,4-Dioxo-5-(2,3,4-trihydroxy-benzylidene)-thiazolidin-3-yl]-acetic acid
20. 5-(4-Diethylamino-2-hydroxy-benzyl)-thiazolidine-2,4-dione
21. 5-[3-(2-Hydroxy-4-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
- 5 22. 5-(2,4,6-Trihydroxy-benzylidene)-thiazolidine-2,4-dione
23. 5-(2-Hydroxy-5-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
24. 5-(2,5-Dihydroxy-benzylidene)-4-imino-thiazolidin-2-one
25. 2-Imino-5-(2-methyl-benzylidene)-thiazolidin-4-one
26. [5-(4-Methoxy-2,3-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
- 10 27. 5-(2,4,6-Trimethyl-benzyl)-thiazolidine-2,4-dione
28. 5-[3-(2,5-Dimethyl-phenyl)-allylidene]-thiazolidine-2,4-dione
29. 5-(4-Methoxy-2,5-dimethyl-benzylidene)-thiazolidine-2,4-dione
30. 5-[3-(4-Methoxy-phenoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
31. 5-[3-(4-*tert*-Butyl-phenoxy)-benzylidene]-4-imino-thiazolidin-2-one
- 15 32. 2-Imino-5-(3-*p*-tolylloxy-benzylidene)-thiazolidin-4-one
33. [5-(3-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
34. 5-(3,4-Dimethoxy-benzyl)-thiazolidine-2,4-dione
35. 5-[3-(3,4,5-Trimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
36. 5-(4-Benzylloxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione
- 20 37. 5-(3,5-Dimethoxy-benzylidene)-4-thioxo-thiazolidin-2-one
38. 5-(3-Benzylloxy-benzylidene)-4-imino-thiazolidin-2-one
39. 5-(3-Hydroxy-benzylidene)-2-imino-thiazolidin-4-one
40. [5-(3-Hydroxy-4-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
41. 5-(3,4-Dihydroxy-benzyl)-thiazolidine-2,4-dione
- 25 42. 5-(3-*m*-Tolyl-allylidene)-thiazolidine-2,4-dione
43. 5-(4-Methoxy-3-methyl-benzylidene)-thiazolidine-2,4-dione
44. 5-(4-Dimethylamino-benzylidene)-4-thioxo-thiazolidin-2-one
45. 5-(4-Diethylamino-benzylidene)-4-imino-thiazolidin-2-one
46. 2-Imino-5-(4-phenoxy-benzylidene)-thiazolidin-4-one
- 30 47. [5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
48. 5-(3-Benzylloxy-4-methoxy-benzyl)-thiazolidine-2,4-dione
49. 5-[3-(4-Benzylloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
50. 5-(4-Ethoxy-benzylidene)-thiazolidine-2,4-dione
51. 5-(4-Butoxy-benzylidene)-4-thioxo-thiazolidin-2-one
- 35 52. 4-Imino-5-naphthalen-1-ylmethylene-thiazolidin-2-one

53. 2-Imino-5-(2-methoxy-naphthalen-1-ylmethylene)-thiazolidin-4-one
54. [5-(2-Hydroxy-naphthalen-1-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
55. 5-(4-Methoxy-naphthalen-1-ylmethyl)-thiazolidine-2,4-dione
- 5 56. 5-(3-Naphthalen-2-yl-allylidene)-thiazolidine-2,4-dione
57. 5-(3,4-Bis-benzyloxy-benzylidene)-thiazolidine-2,4-dione
58. 5-(9-Ethyl-9*H*-carbazol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
59. 4-Imino-5-(1*H*-indol-3-ylmethylene)-thiazolidin-2-one
60. 2-Imino-5-(5-methoxy-1*H*-indol-3-ylmethylene)-thiazolidin-4-one
- 10 61. (5-Benzo[1,3]dioxol-5-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
62. 5-Quinolin-4-ylmethyl-thiazolidine-2,4-dione
63. 5-[3-(4-Hydroxy-phenyl)-allylidene]-thiazolidine-2,4-dione
64. 5-(4-Hydroxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione
65. 5-(4-Hydroxy-3,5-dimethoxy-benzylidene)-4-thioxo-thiazolidin-2-one
- 15 66. 5-(3-Ethoxy-4-hydroxy-benzylidene)-4-imino-thiazolidin-2-one
67. 5-(4-Hydroxy-3,5-dimethyl-benzylidene)-2-imino-thiazolidin-4-one
68. (5-Biphenyl-4-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
69. 5-(4-Methylsulphanyl-benzyl)-thiazolidine-2,4-dione
70. 5-[3-(4-Isopropyl-phenyl)-allylidene]-thiazolidine-2,4-dione
- 20 71. 5-(4-Methyl-benzylidene)-thiazolidine-2,4-dione
72. 5-(4-Ethyl-benzylidene)-4-thioxo-thiazolidin-2-one
73. 5-(2,2-Diphenyl-ethylidene)-4-imino-thiazolidin-2-one
74. [5-(2-Methyl-3-phenyl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
75. 5-(2-Pentyl-3-phenyl-allyl)-thiazolidine-2,4-dione
- 25 76. 5-(4-Hexyl-5-phenyl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
77. 5-Phenethylidene-thiazolidine-2,4-dione-2-one
78. 4-Imino-5-(3-phenyl-allylidene)-thiazolidin-2-one
79. 2-Imino-5-[3-(2-methoxy-phenyl)-allylidene]-thiazolidin-4-one
80. {5-[3-(4-Dimethylamino-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
- 30 acid
81. 5-(3-Phenyl-propyl)-thiazolidine-2,4-dione
82. 5-[3-(3,5-Di-*tert*-butyl-4-hydroxy-phenyl)-allylidene]-thiazolidine-2,4-dione
83. 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethylene)-thiazolidine-2,4-dione
84. 5-(3-Ethoxy-4-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
- 35 85. 5-(4-Diethoxymethyl-benzylidene)-4-imino-thiazolidin-2-one

86. 5-(4-Dimethylamino-naphthalen-1-ylmethylene)-2-imino-thiazolidin-4-one
87. 5-(2,4-Dimethoxy-3-methyl-benzyl)-thiazolidine-2,4-dione
88. 5-(4-Styryl-benzylidene)-thiazolidine-2,4-dione
89. 5-[4-(3-Dimethylamino-propoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
5 90. 5-(2,4-Dihydroxy-benzylidene)-4-imino-thiazolidin-2-one
91. 2-Imino-5-(2-methyl-1*H*-indol-3-ylmethylene)-thiazolidin-4-one
92. [5-(4-Hydroxy-3-methyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
93. 5-(2-Hexyloxy-benzyl)-thiazolidine-2,4-dione
94. 5-(4-Allyloxy-benzylidene)-thiazolidine-2,4-dione
10 95. 5-(4-Propoxy-benzylidene)-4-thioxo-thiazolidin-2-one
96. 4-Imino-5-(4-pentyloxy-benzylidene)-thiazolidin-2-one
97. 2-Imino-5-(4-octyloxy-benzylidene)-thiazolidin-4-one
98. [5-(5-Benzoyloxy-1*H*-indol-3-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
99. 5-Benzofuran-2-ylmethyl-thiazolidine-2,4-dione
15 100. 5-(4-Pyrrolidin-1-yl-benzylidene)-thiazolidine-2,4-dione
101. 5-(2,3,4,5,6-Pentamethyl-benzylidene)-4-thioxo-thiazolidin-2-one
102. 5-(2-Benzoyloxy-benzylidene)-4-imino-thiazolidin-2-one
103. 2-Imino-5-(2,3,4-trimethoxy-6-methyl-benzylidene)-thiazolidin-4-one
104. [5-(3-Ethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
20 105. 5-(3,4-Dihydroxy-5-methoxy-benzyl)-thiazolidine-2,4-dione
106. 5-(3,5-Dihydroxy-benzylidene)-thiazolidine-2,4-dione
107. 5-(3,4-Dimethyl-benzylidene)-4-thioxo-thiazolidin-2-one
108. 5-(4-Ethoxy-3-methoxy-benzylidene)-4-imino-thiazolidin-2-one
109. [5-(4-Heptyloxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
25 110. 5-Benzo[1,3]dioxol-4-ylmethyl-thiazolidine-2,4-dione
111. 5-[3-(4-Methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
112. 4-Thioxo-5-(2,4,5-trimethyl-benzylidene)-thiazolidin-2-one
113. 5-(4-Decyloxy-benzylidene)-4-imino-thiazolidin-2-one
114. [5-(4-*tert*-Butyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
30 115. (3-Allyl-2-hydroxy-benzylidene)-4-thioxo-thiazolidin-2-one
116. 5-(4-Amino-benzylidene)-4-imino-thiazolidin-2-one
117. [5-(4-Butyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
118. 5-(4-*tert*-Butoxy-benzyl)-thiazolidine-2,4-dione
119. 5-(4-Propyl-benzylidene)-thiazolidine-2,4-dione
35 120. 5-(4-Hexyl-benzylidene)-4-thioxo-thiazolidin-2-one

121. 4-Imino-5-(4-octyl-benzylidene)-thiazolidin-2-one
122. [2,4-Dioxo-5-(4-pentyl-benzylidene)-thiazolidin-3-yl]-acetic acid
123. 5-(3-Amino-benzyl)-thiazolidine-2,4-dione
124. 5-(2-Ethoxy-naphthalen-1-ylmethylene)-thiazolidine-2,4-dione
- 5 125. 5-(7-Methyl-1*H*-indol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
126. 5-[3-(4-*tert*-Butyl-phenyl)-2-methyl-propylidene]-4-imino-thiazolidin-2-one
127. [5-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid 5-(4-Hydroxy-2-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
128. 5-(2,2-Dimethyl-chroman-6-ylmethylene)-4-imino-thiazolidin-2-one
- 10 129. 5-(4-Methyl-naphthalen-1-ylmethyl)-thiazolidine-2,4-dione
130. 5-(3-Furan-2-yl-2-methyl-allylidene)-thiazolidine-2,4-dione; propylidene-2-one; 5-(2,3-Dihydro-benzofuran-5-ylmethylene)-4-imino-thiazolidin-2-one
131. {5-[3-(4-Diethylamino-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
132. 5-(4-Isobutyl-benzyl)-thiazolidine-2,4-dione
- 15 133. 5-[3-(4-Hydroxy-3-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
134. 5-(6-Methoxy-naphthalen-2-ylmethylene)-4-thioxo-thiazolidin-2-one
135. 5-(3,5-Dimethyl-benzylidene)-4-imino-thiazolidin-2-one
136. [2,4-Dioxo-5-(4-phenylethynyl-benzylidene)-thiazolidin-3-yl]-acetic acid
137. 5-[3-(4-*tert*-Butyl-phenyl)-2-methyl-allylidene]-thiazolidine-2,4-dione
- 20 138. 5-(4-Octadecyloxy-benzylidene)-4-thioxo-thiazolidin-2-one
139. 5-(4-Diphenylamino-benzylidene)-4-imino-thiazolidin-2-one
140. [5-(4-Dimethylamino-2-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
141. 5-(2-Benzoyloxy-4,5-dimethoxy-benzyl)-thiazolidine-2,4-dione
- 25 142. 5-[3-(2-Hydroxy-ethoxy)-benzylidene]-thiazolidine-2,4-dione
143. 5-[2-(2-Hydroxy-ethoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
144. 5-[4-(2-Hydroxy-ethoxy)-benzylidene]-4-imino-thiazolidin-2-one
145. [5-(4-*tert*-Butoxycarbonyloxy-3-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
- 30 146. 5-[3-(4-Hydroxy-3,5-dimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
147. 5-(2-Benzoyloxy-3-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
148. 4-Imino-5-(4-methanesulphonyl-benzylidene)-thiazolidin-2-one
149. (5-Benzo[*b*]thiophen-2-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
150. 5-(3-Benzo[*b*]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione
- 35 151. 5-Thiophen-2-ylmethylene-4-thioxo-thiazolidin-2-one

152. 4-Imino-5-(3-naphthalen-2-yl-allylidene)-thiazolidin-2-one
153. [5-(2-[1,3]Dioxolan-2-yl-6-fluoro-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
154. 5-(2,4-Bis-benzyloxy-benzylidene)-thiazolidine-2,4-dione
- 5 155. 5-(4-Benzyl-benzylidene)-4-thioxo-thiazolidin-2-one
156. 5-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenylidene]-4-imino-thiazolidin-2-one
157. (5-Furan-2-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
158. 5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione
- 10 159. 5-(1-Methyl-1*H*-pyrrol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
160. 5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-4-imino-thiazolidin-2-one
161. [5-(5-Benzylloxy-2-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
162. 5-(4-Benzylloxy-3,5-dimethoxy-benzylidene)-thiazolidine-2,4-dione
163. 5-(4-Benzylloxy-3,5-dihydroxy-benzylidene)-4-thioxo-thiazolidin-2-one
- 15 164. 5-(2,5-Bis-benzyloxy-benzylidene)-4-imino-thiazolidin-2-one
165. (5-Cyclohexylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
166. 5-(3-Biphenyl-4-yl-allylidene)-thiazolidine-2,4-dione
167. 5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-4-thioxo-thiazolidin-2-one
168. 5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-4-imino-thiazolidin-2-one
- 20 169. 2-(3-Carboxymethyl-2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
170. 5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-2-hydroxy-benzoic acid
171. Methyl 4-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoate
172. 4-(4-Imino-2-oxo-thiazolidin-5-ylidenemethyl)-benzoic acid
173. [2,4-Dioxo-5-(4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidin-3-yl]-acetic acid
- 25 174. [4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid
175. 3-(2-Oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
176. 4-(4-Imino-2-oxo-thiazolidin-5-ylidenemethyl)-phenyl propionate
177. [5-(2-Ethoxycarbonylmethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
- 30 178. 8-(2,4-Dioxo-thiazolidin-5-ylmethyl)-naphthalene-1-carboxylic acid
179. 5-(6-Methyl-4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidine-2,4-dione
180. 2-Acetoxy-5-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-phenyl acetate
181. 5-(2-Amino-4-oxo-4*H*-chromen-3-ylmethylene)-4-imino-thiazolidin-2-one
182. [5-(6-Ethyl-4-oxo-4*H*-chromen-3-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
- 35

183. 5-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-ylmethyl)-thiazolidine-2,4-dione
184. 5-(6-Isopropyl-4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidine-2,4-dione
185. Methyl 2-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoate
186. Methyl 3-(4-imino-2-oxo-thiazolidin-5-ylidenemethyl)-1*H*-indole-6-carboxylate
5 187. [2,4-Dioxo-5-(1-phenyl-ethylidene)-thiazolidin-3-yl]-acetic acid
188. 5-(1-*p*-Tolyl-ethyl)-thiazolidine-2,4-dione
189. 5-[1-(4-Methoxy-phenyl)-ethylidene]-thiazolidine-2,4-dione
190. 5-[1-(3,4-Dichloro-phenyl)-ethylidene]-4-thioxo-thiazolidin-2-one
191. 4-Imino-5-(1-thiophen-2-yl-ethylidene)-thiazolidin-2-one
10 192. 5-(4-Ethoxy-3-methoxy-benzylidene)-2-imino-thiazolidin-4-one
193. 5-(4-Decyloxy-benzylidene)-2-imino-thiazolidin-4-one
194. 5-(4-Amino-benzylidene)-2-imino-thiazolidin-4-one
195. 2-Imino-5-(4-octyl-benzylidene)-thiazolidin-4-one
196. 5-(2,2-Dimethyl-chroman-6-ylmethylene)-2-imino-thiazolidin-4-one
15 197. 5-(2,3-Dihydro-benzofuran-5-ylmethylene)-2-imino-thiazolidin-4-one
198. 5-(3,5-Dimethyl-benzylidene)-2-imino-thiazolidin-4-one
199. 5-(4-Diphenylamino-benzylidene)-2-imino-thiazolidin-4-one
200. 5-[4-(2-Hydroxy-ethoxy)-benzylidene]-2-imino-thiazolidin-4-one
201. 2-Imino-5-(4-methanesulphonyl-benzylidene)-thiazolidin-4-one
20 202. 2-Imino-5-(3-naphthalen-2-yl-allylidene)-thiazolidin-4-one
203. 5-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenylidene]-2-imino-thiazolidin-4-one
204. 5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-2-imino-thiazolidin-4-one
205. 5-(2,5-Bis-benzyloxy-benzylidene)-2-imino-thiazolidin-4-one
25 206. 5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-2-imino-thiazolidin-4-one
207. 4-(2-Imino-4-oxo-thiazolidin-5-ylidenemethyl)-benzoic acid
208. 4-(2-Imino-4-oxo-thiazolidin-5-ylidenemethyl)-phenyl propionate
209. 5-(2-Amino-4-oxo-4*H*-chromen-3-ylmethylene)-2-imino-thiazolidin-4-one
210. Methyl 3-(2-imino-4-oxo-thiazolidin-5-ylidenemethyl)-1*H*-indole-6-carboxylate
30 211. 2-Imino-5-(1-thiophen-2-yl-ethylidene)-thiazolidin-4-one
212. {5-[1-(3,5-Dihydroxy-phenyl)-ethylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
213. 5-(2,4-Bis-benzyloxy-benzyl)-thiazolidine-2,4-dione
214. 5-Pyridin-2-ylmethyl-thiazolidine-2,4-dione
215. 5-(4-Benzyloxy-3,5-dimethoxy-benzyl)-thiazolidine-2,4-dione
35 216. 5-(2,4-Dioxo-thiazolidin-5-ylmethyl)-2-hydroxy-benzoic acid

217. [4-(2,4-Dioxo-thiazolidin-5-ylmethyl)-phenoxy]-acetic acid
218. 5-[3-(2,4-Dimethoxy-3-methyl-phenyl)-allylidene]-thiazolidine-2,4-dione
219. 5-[3-(2-Hexyloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
220. 5-(3-Benzofuran-2-yl-allylidene)-thiazolidine-2,4-dione
5 221. 5-[3-(3,4-Dihydroxy-5-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
222. 5-(3-Benzo[1,3]dioxol-4-yl-allylidene)-thiazolidine-2,4-dione
223. 5-[3-(4-*tert*-Butoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
224. 5-[3-(3-Amino-phenyl)-allylidene]-thiazolidine-2,4-dione 5-(5-Furan-2-yl-4-methyl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
10 225. 5-[5-(4-Hydroxy-3-methoxy-phenyl)-penta-2,4-dienylidene]-thiazolidine-2,4-dione
226. 5-[5-(4-*tert*-Butyl-phenyl)-4-methyl-penta-2,4-dienylidene]-thiazolidine-2,4-dione
227. 5-{3-[3-(2-Hydroxy-ethoxy)-phenyl]-allylidene}-thiazolidine-2,4-dione
15 228. 5-[5-(4-Hydroxy-3,5-dimethoxy-phenyl)-penta-2,4-dienylidene]-thiazolidine-2,4-dione
229. 5-(5-Benzo[*b*]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
230. 5-[3-(2,4-Bis-benzyloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
231. 5-(3-Pyridin-2-yl-allylidene)-thiazolidine-2,4-dione
20 232. 5-[3-(4-Benzyloxy-3,5-dimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
233. 5-(5-Biphenyl-4-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
234. 5-[3-(2,4-Dioxo-thiazolidin-5-ylidene)-propenyl]-2-hydroxy-benzoic acid
235. 3-[3-(2,4-Dioxo-thiazolidin-5-ylidene)-propenyl]-benzoic acid
236. 2-Acetoxy-5-[3-(2,4-dioxo-thiazolidin-5-ylidene)-propenyl]-phenyl acetate
25 237. Methyl 2-[3-(2,4-dioxo-thiazolidin-5-ylidene)-propenyl]-benzoate
238. 5-[3-(3,4-Dichloro-phenyl)-but-2-enylidene]-thiazolidine-2,4-dione

The following Examples show some process variants which can be used for the synthesis of the compounds in accordance with the invention. However, they are not intended to be a limitation of the object of the invention. The structure of the compounds was proven by ¹H- and, where necessary, by ¹³C-NMR spectroscopy. The purity of the substances was determined by C, H, N, P analysis as well as by thin-layer chromatography.

Example 1**General Process A:**

A solution of 5.4 mmol of aldehyde of the formula R-CHO, wherein R has the
5 significance given above, and 5.4 mmol of thiazolidine-2,4-dione in 30 ml of abs.
toluene is treated with catalytic amounts of piperidinium acetate and heated at reflux
for 5 to 10 hours. Thereafter, the mixture is cooled to 0°C. The precipitate is filtered off
under suction, rinsed with diethyl ether and dried.

10 **5-Benzylidene-thiazolidine-2,4-dione (1)**

Colourless crystals; m.p. 241-3°C

5-(2-Hydroxy-benzylidene)-thiazolidine-2,4-dione (2)

Dark yellow crystals; m.p. 249-51°C

15

5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dione (3)

Pale yellow crystals; m.p. 213-5°C

5-(3,4-Dimethoxy-benzylidene)-thiazolidine-2,4-dione (4)20

Yellow crystals; 215-7°C

5-Benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione (5)

Yellow crystals; 248-9°C

25 **5-(4-Isopropyl-benzylidene)-thiazolidine-2,4-dione (6)**

Colourless crystals; m.p. 149-51°C

5-(4-Dimethylamino-benzylidene)-thiazolidine-2,4-dione (7)

Red-brown crystals; m.p. >280°C

30

5-Naphthalen-2-ylmethylene-thiazolidine-2,4-dione (8)

Yellow crystals; m.p. 196-8°C

5-Phenthylidene-thiazolidine-2,4-dione (9)

Colourless crystals; m.p. >280°C

5-[2-(2-Hydroxy-phenyl)-ethylidene]-thiazolidine-2,4-dione (10)

5 Yellow crystals (sic); m.p. 212-5°C (dec.)

5-[2-(3,4-Dimethoxy-phenyl)-ethylidene]-thiazolidine-2,4-dione (11)

Pale yellow crystals; m.p. 282-5°C (dec.)

10 **5-[2-(4-Isopropyl-phenyl)-ethylidene]-thiazolidine-2,4-dione (12)**

Beige crystals; m.p. >280°C

5-[2-(4-Dimethylamino-phenyl)-ethylidene]-thiazolidine-2,4-dione (13)

Orange-yellow crystals; m.p. >280°C

15

5-Thiophen-2-ylmethylene-thiazolidine-2,4-dione (14)

Yellow crystals; m.p. >280°C

5-Thiophen-3-ylmethylene-thiazolidine-2,4-dione (15)

20 Beige crystals; m.p. >280°C

5-Naphthalen-1-ylmethylene-thiazolidine-2,4-dione (16)

Pale yellow crystals; m.p. >280°C

25 **5-(1H-Indol-3-ylmethylene)-thiazolidine-2,4-dione (17)**

Yellow crystals; m.p. >280°C

5-(4-Benzyloxy-benzylidene)-thiazolidine-2,4-dione (18)

Beige crystals; m.p. 215-8°C

30

5-Furan-2-ylmethylene-thiazolidine-2,4-dione (19)

Beige crystals; m.p. 228-30°C

5-(4-Propionyl-benzylidene)-thiazolidine-2,4-dione (20)

35 Pale yellow crystals; m.p. 182-5°C

5-Benzo[b]thiophen-2-ylmethylene-thiazolidine-2,4-dione (21)

Yellow crystals; m.p. >240°C

5 5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione (22)

Yellow crystals; m.p. >240°C

5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione (23)

Brown crystals; m.p. 210°C (dec.)

10

5-(3-Phenoxy-benzyl)-thiazolidine-2,4-dione (24)

Beige crystals; m.p. 207°C (dec.)

5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-thiazolidine-2,4-dione (25)

15 Orange-red crystals; m.p. 253-5°C

5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-thiazolidine-2,4-dione (26)

Yellow crystals; m.p. 193-6°C

20 Example 2

General Process B:

14 mmol of aldehyde of the formula R-CHO, wherein R has the given significance, and
10 mmol of ethyl 2,4-dioxo-thiazolidin-3-ylacetate (Pharmazie 40 727-8 (1985)) are
25 heated under reflux together with 30 mmol of sodium acetate and 40 ml of glacial acetic
acid for 6-18 hours. After cooling the mixture is poured into H₂O. The precipitate is
filtered off under suction, rinsed with H₂O and dried. For purification, it is
chromatographed over silica gel with ethyl acetate/heptane.

**30 Ethyl 5-3-(5,6-diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-
acetate (27)**

Orange crystals; m.p. 193-5°C

Ethyl 5-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetate
(28)

Yellow crystals; m.p. 138-41°C

5 Methyl 5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetate
(29)

Yellow crystals; m.p. 70-5°C

Methyl 5-(3,4-Dihydroxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-
acetate (30)

10 Ochre-coloured crystals; m.p. 220-3°C

Methyl 5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-
3-yl-acetate (31)

Ochre coloured crystals; m.p. 160-4°C

15

Example 3

General Process C:

7 mmol of the corresponding ethyl acetate derivative are then treated with 0.4 ml of
20 sulphuric acid and 18 ml of formic acid. The formic acid is removed in a vacuum and
the residue is recrystallized from water/acetonitrile.

[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
(32)

25 Pale yellow crystals; m.p. 130-5°C

[5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
(33)

Colourless crystals; m.p. 180-3°C

30

[5-(3,4-Dihydroxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
(34)

Yellow crystals; m.p. 230°C (dec.)

5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (35)

Orange crystals; m.p. 235°C (dec.)

5 5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (36)

Orange crystals; m.p. 135°C (dec.)

10 5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (37)

Yellow crystals; m.p. 190-3°C

[5-(3-Biphenyl-4-yl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (38)

Orange crystals; m.p. 215°C (dec.)

15

Example 4

General Process D:

20 a. 10 mmol of 4-thioxo-thiazolidin-2-one (Chem. Heterocycl. Compds. EN 3 533-4 (1967) and 10 mmol of aldehyde R-CHO, wherein R has the given significance, are taken up in 10 ml of glacial acetic acid, treated with 1 g of sodium acetate and heated at reflux for 10-60 min. After cooling 10 ml of H₂O are added thereto, the precipitate is filtered off and rinsed with H₂O and dried. For purification, it is recrystallized from (sic) methanol.

25

b. 10 mmol of the corresponding 5-alkyl-4-thioxo-thiazolidin-2-one derivative are treated with 3.25 mmol of P₂S₅ in 10 ml of abs. dioxan for 3 to 10 hours. Thereafter, active charcoal is added and the mixture is heated for a further 30 min. The mixture is filtered and the solvent is removed under a vacuum.
30 The residue is recrystallized from water.

Example 5**General Process E:**

- 5 a. 10 mmol of 4-iminothiazolidin-2-one one (Chem. Heterocycl. Compds. EN 4
324-5 (1968)) and 10 mmol of aldehyde R-CHO, wherein R has the given
significance, are treated with 1 g of sodium acetate and 10 ml of glacial acetic
acid. The mixture is heated at reflux for 10 to 60 min., cooled and poured into
60 ml of water. The precipitate is filtered off under suction, rinsed with water
10 and methanol and dried.
- b. 10 mmol of the corresponding 5-alkylidene-4-thioxo-thiazolidin-2-one
derivative are heated to 100°C with 6 ml of conc. Ammonia for 10 to 60 min.
After cooling the precipitate is filtered off under suction and rinsed with water
15 and methanol. For purification, it is crystallized from dioxan.

Example 6**General process F:**

- 20 10 mmol of the corresponding 5-alkylidene-2,4-thiazolidinedione derivative are
hydrogenated in tetrahydrofuran with 1 g of Pd/C 10% at 50 PSI. The catalyst is filtered
off and the solvent is removed in a vacuum.. The residue is purified by chromatography
over silica gel (heptane/ethyl acetate).

25 **Example 7**

Compounds of general formula (I) were investigated in a suitable assay for the
capability of stimulating cyclic adenylyl cyclase.

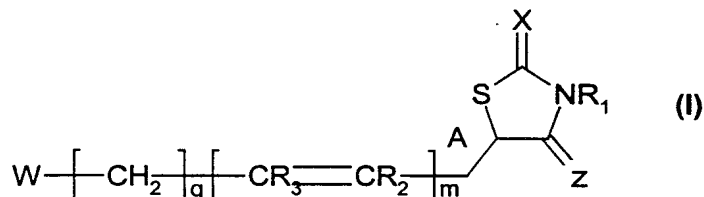
Table I:

Example No.	Name	% cAMP (test conc. 50μM)
<u>22</u>	5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione	15
<u>23</u>	5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione	30
<u>32</u>	[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid	15
<u>36</u>	5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid	20

Patent Claims

1. Use of Compounds of general formula (I)

5



in which

m signifies a number between 0-8,

10 q signifies a number between 0-8

A signifies a single or double bond

R₁ signifies hydrogen or, when X and Z are oxygen, also -CH₂)-COR₄ with a = 0-6R₂, R₃ signify hydrogen or lower alkyl,15 whereby R₂ and R₃ can be the same or different and, when m signifies 2-8, R₂ and R₃ in the group CR₂=CR₃ can have various significances within the following sequenceR₄ signifies hydroxyl, lower alkoxy or the NR₁R₂ residue, whereby R₁ and R₂ can be the same or different

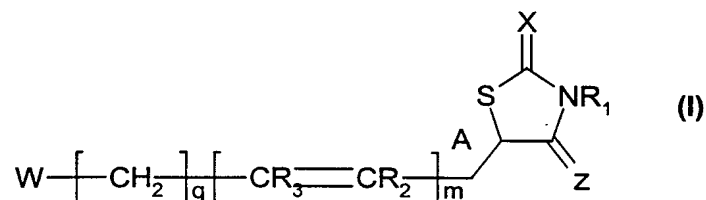
20 X signifies oxygen or imino

Z signifies oxygen, sulphur or imino

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

25 for the preparation of medicaments for the treatment and prevention of metabolic bone disorders,

2. Compounds of general formula (I)



5

in which

m signifies a number between 0-8,

q signifies a number between 0-8

A signifies a single or double bond

10 R₁ signifies hydrogen or, when X and Z are oxygen, also -CH₂)-COR₄ with a = 0-6

R₂, R₃ signify hydrogen or lower alkyl,

whereby R₂ and R₃ can be the same or different and, when m signifies 2-8, R₂ and R₃ in the group CR₂=CR₃ can have various significances within the following

15 sequence

R₄ signifies hydroxyl, lower alkoxy or the NR₁R₂ residue, whereby R₁ and R₂ can be the same or different

X signifies oxygen or imino

Z signifies oxygen, sulphur or imino

20 W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl, naphthyl, indolyl, benzofuranyl and benzothiophen-yl, if X signifies oxygen, m and q are both 0 and R₁ is hydrogen,

25

whereas W is not an aminosubstituted phenyl and indolyl, if X signifies imino, m and q both are 0 and R₁ is hydrogen,

as well as their physiologically compatible salts, esters, optically active forms,

30 racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I).

3. Medicament containing at least one compound of general formula (I) according to claim 2 in admixture with usual pharmaceutical adjuvants and carrier material

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/EP 99/07252

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/34 C07D417/06 A61K31/425 C07D277/36 C07D277/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. STEFANOVIC ET AL: "The synthesis of alpha-methyl-beta-phenylisocysteine and the preparation of substituted thiazolidine-5-carboxylic acids" TETRAHEDRON., vol. 18, 1962, pages 413-418, XP002093194 OXFORD GB * page 414, compound II, page 416* ----- -/--	2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 January 2000

Date of mailing of the international search report

14/01/2000

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INTERNATIONAL SEARCH REPORT

Inter. Application No.

PCT/EP 99/07252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 76, no. 25, 19 June 1972 (1972-06-19) Columbus, Ohio, US; abstract no. 153658q, A.I. GINAK ET AL: "Synthesis of 2,4-thiazolidinediones" page 459; XP002093196 abstract & ZH. PRIKL. KHIM., vol. 45, no. 2, 1972, pages 460-462, Leningrad ---	2
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INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/EP 99/07252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 55, no. 18, 4 September 1961 (1961-09-04) Columbus, Ohio, US; abstract no. 17623c, V.G. ZUBENKO: "Synthesis of 5-arylidene derivatives of 2,4-thiazolidinedione" XP002093199 abstract & TRUDY L'VOV MED INST., vol. 12, 1957, pages 80-82, ---	2
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X	US 5 143 929 A (BELLIOTTI THOMAS R ET AL) 1 September 1992 (1992-09-01) the whole document ---	1,2
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 434 394 A (ELI LILLY AND COMPANY) 26 June 1991 (1991-06-26) claims ----	1,2
X	EP 0 398 179 A (NISSHIN FLOUR MILLING CO) 22 November 1990 (1990-11-22) claims ----	1,2
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/07252

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: partially 2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: partially 2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim 2 (compounds per se) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Consequently, the search report with regard to said claim 2 has been limited to a selection of retrieved novelty-affecting documents with special emphasis to the compounds 1-38 of examples 1-3 and to compounds mentioned pages 9-16 of the description (compounds 1-238).

It should however be noted that the search and the search report can be considered as covering all claimed compounds of the prior art insofar those display an activity for treatment and the prevention of metabolic bone disorders.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07252

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07252

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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